IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Saxinger

Application No. 10/084,813

Art Unit: 1648

Examiner: Jeffrey S. Parkin

Filed: February 27, 2002

For: POLYPEPTIDES THAT BIND HIV gp120 AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

DECLARATION UNDER 37 C.F.R. § 1.132 OF CARL SAXINGER, PH.D.

I, Carl Saxinger, Ph.D. do hereby declare that:

1. I am the sole inventor of the subject matter disclosed and claimed in the instant application. I have been actively engaged in research in the relevant art since a time prior to the filing of the instant application, and I am familiar with level of skill in the art and the general knowledge that was available to the person of ordinary skill in the art at that time.

2. The pending claims of the instant application are directed to a polypeptide that comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-15, with up to 6 conservative or neutral amino acid substitutions. The claims require that the polypeptide binds with HIV gp120 under physiological conditions.

3. As described in my prior Rule 132 Declaration dated July 31, 2005, the instant application provides guidance as to which amino acids are required for binding activity. In particular, Example 1 illustrates that SEQ ID NOs: 12-15 bind with high affinity to HIV gp120. Example 1 also shows that amino acid sequences comprising only certain portions of SEQ ID NOS: 12-15 also bind to HIV gp120 with relatively high affinity, but that other amino acid sequences that comprise a different portion of SEQ ID NOs: 12-15 do not share the same binding affinity with HIV gp120. The sequences tested in Example 1 correspond to SEQ ID NOs: 12-15 as follows: SEQ

ID NOs: 50-59 correspond (in part) to SEQ ID NO: 12; SEQ ID NOs: 73-81 correspond (in part) to SEQ ID NO: 13; SEQ ID NOs: 89-98 correspond (in part) to SEQ ID NO: 14; SEQ ID NOs: 101-109 correspond (in part) to SEQ ID NO: 15. A more detailed correlation of the tested sequences to the claimed sequences is provided in the prior Rule 132 Declaration.

4. By comparing the tested sequences that retain binding affinity to those that do not retain binding affinity, one of ordinary skill in the art during the relevant time reading the application would have been able to discern which amino acid residues of SEQ ID NOS: 12-15 are required for binding activity. For example, from the information on binding activity provided in Example 1, as summarized above, the ordinarily skilled artisan would have been able to determine that the residues "LLTG" of SEQ ID NO: 12, the residues "SQYQ" of SEQ ID NO: 13, and the residues "LLNT" of SEQ ID NO: 14 are most important for binding activity. Similarly, the data shows that SEQ ID NO: 15 contains two sub-sequences of residues involved in binding "FVGE" and "FFQK" contained within the larger sub-sequence "FVGEKFRNYLLVFFQK." Example 1, thus, provides specific guidance as to which amino acid residues are the most likely candidates for conservative or neutral amino acid substitutions.

5. Example 1 of the instant application also provides some evidence of binding activity in the presence of flanking sequences in at least two respects. First, the binding activity of the receptor peptides described therein was conducted in the context of a 100 unit long polylysine backbone. The procedure used is similar to that discussed in Saxinger et al., *BMC Immunology, 6,* 1-15 (2005) (copy enclosed). In this respect, every sequence described in Example 1 was tested as part of a larger construct with a "flanking" lysine connecting the sequence to a polylysine molecule.

6. Second, the sequences described in Example 1 were tested as a transitioning sequence offset (four amino acids offset at a time) to show which sequence motifs were most important to the binding activity. This is apparent by reading down the list of sequences tested in Example 1, wherein each successive sequence contains part of the sequence before it modified such that four amino acids are removed from the amino-end of the sequence, and four amino acids are added to the carboxy-end of the sequence.

7. In this respect, Example 1 demonstrates the addition of "flanking" amino acids to the binding sequences of the molecule by effectively adding amino acids to one end of the claimed sequences, while removing amino acids from the other. For instance, SEQ ID NO: 53 tested in Example 1 shows that adding the amino acid residues "YAAA" to the amino-end of SEQ ID NO: 12 does not abrogate binding activity. Similarly, SEQ ID NO: 56 tested in Example 1 shows that adding "GIFF" to the carboxy-end of SEQ ID NO: 12 does not abrogate binding activity. As the transitioning of SEQ ID NO: 12 progresses (e.g., to SEQ ID NOs: 52 or 57, the amino acids important for binding (e.g., "SYQY") are removed, thereby abrogating activity. Similarly, SEQ ID NOs: 92 and 95 tested in Example 1 show the effect of adding, respectively, the sequences "FLFW" to the amino-end of the SEQ ID NO: 14 and "SSNR" to the carboxyl-end of the SEQ ID NO: 14. SEQ ID NOs: 74-76 tested in Example 1 show the effect of adding amino acids to the amino-end of SEQ ID NO: 13, and SEQ ID NOs: 103 and 104 show the effect of adding amino acids to the amino-end of SEQ ID NO: 15. No examples, however, are provided that show the effect of adding amino acids to the carboxyl terminus of SEQ ID NOs: 13 or 15 because, as transitioning progressed, the amino acids most involved in binding that were located near the amino terminus were removed, thereby abrogating binding activity.

8. Furthermore, it was well within the skill of the ordinary researcher at the relevant time to determine whether any given flanking sequence would disrupt the biological activity of SEQ ID NOs: 12-15 using no more than routine experimentation and the general knowledge then available.

9. During the relevant period of time, research scientists routinely placed core binding sequences, such as SEQ ID NOs: 12-15, within a larger molecule for a variety of reasons. For example, larger polypeptides could be designed to include multiple copies of a sequence of interest so as to create a molecule with increased binding activity. Also, facilitating or associating sequences generally known in the art at the time could be placed in proximity to the core sequence to modulate the activity of the core sequence. Similarly, known targeting sequences could be placed in proximity to the core sequence to direct the polypeptide to a particular tissue or cell type. Furthermore, increasing the length of the polypeptide can stabilize the core sequence (e.g., by increasing *in vivo* half-life).

10. Examples of such constructs, whereby a core sequence with an identified biological activity is utilized as part of a larger construct, are commonplace in the art (e.g., Reeves et al., *J. General Virology, 79,* 1793-99 (1998) (copy enclosed)).

11. It would be the rare instance, that a chosen flanking sequence would have exactly the primary, secondary, and tertiary structure needed to block the activity of the core binding sequence. Furthermore, during the relevant period of time, the effect of a given flanking sequence on the binding activity of the core sequence could be predicted based on the chemical properties of the amino acid residues involved. These chemical properties are widely known and well understood, and have been since a time long before the present application was filed. Indeed, computer modeling programs were readily available during that time that could show any predictable conformational changes that would be caused by the addition of flanking sequences.

12. Thus, it was well within the skill of the ordinary researcher at the relevant time to choose appropriate flanking sequences that would not abrogate the binding activity of SEQ ID NOs: 12-15. After selecting appropriate candidate flanking sequences, routine and simple tests could have been used by such a researcher to confirm that the molecule retains the intended biological properties.

13. I hereby each declare that all statements made herein of our own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5/23/06

Carl Saxinger

Carl Saxinger, Ph.D.